

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY



(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 05 JAN 2005

WIPO

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Applicant's or agent's file reference IB/G-3259A/ABR		<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/EP2004/000683		International filing date (day/month/year) 27.01.2004		Priority date (day/month/year) 28.01.2003
International Patent Classification (IPC) or national classification and IPC C07D501/00, C07D499/00, C07D477/20				
Applicant SANDOZ AG				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  21.07.2004		Date of completion of this report  04.01.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer  Helps, I  Telephone No. +49 89 2399-8209 		

**INTERNATIONAL PRELIMINARY REPORT  
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International application No.  
PCT/EP2004/000683

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-35 as originally filed

**Claims, Numbers**

1-15 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. IV Lack of unity of invention**

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1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
  - ☐ paid additional fees.
  - ☐ paid additional fees under protest.
  - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
  - ☒ the parts relating to claims Nos. 1-15 (part) .

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-15
Industrial applicability (IA)	Yes: Claims	1-13,15
	No: Claims	14 see below

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item IV.**

Beta-lactams having their carboxy groups esterified by active ester groups giving improved bioavailability have been described in several prior art documents. Since at least the 1-(2-amino-alkoxycarbonyloxy)-ethyl esters of penicillins appear to be known e.g. from GB-A-1,426,717 and have been disclaimed, there is a **priori** lack of unity because there is no common structural feature which renders each of the compounds novel over the respective prior art. Invention 1 is drawn to 2,3-disubstituted 1-propoxycarbonyloxy or 1,3-disubstituted 2-propoxycarbonyloxy ethyl esters which are characterised by the presence of two OH or alkoxycarbonyloxy groups. Invention 2 is characterised by the presence of specific bicyclic groups on the ester, and invention 3 is characterised by the 1-(2-aminoalkoxycarbonyloxy) ethyl group, but with the esters of penicillins disclaimed. Thus there are three groups of compounds each with a distinct characterising feature. This opinion is drawn for the first invention.

**Re Item V.**

1 The following documents are referred to in this communication:

WO-A-99 41275	(A)
GB-A-1,598,568	(B)
JP-A-2000 239275	(C)
US-A-4,486,425	(D)
US-A-4,874,856	(E)
GB-A-1,426,717	(F)

2 Claim 1 is rendered novel by the presence of the 1-(2,3-disubstituted 1-propoxycarbonyloxy)-ethyl or the 1-(1,3-disubstituted 2-propoxycarbonyloxy)-ethyl ester of the carboxylic acid group. The dependent claims 2 to 8 are therefore also novel.

Claim 9 which is drawn to the use of compounds of claim 1 as pharmaceuticals is also rendered novel by the structural feature mentioned above.

Claim 10 which is drawn to compounds of claim 1 for the preparation of pharmaceuticals is also rendered novel by this structural feature.

Claim 11 which is drawn to pharmaceutical compositions containing compounds of claim 1 is also rendered novel by the ester group defined in claim 1. The dependent claims 12 and 15 are therefore also novel.

Claim 13 is rendered novel by the same ester groups referred to in claim 1 and their use in pharmaceutically active compounds.

Claim 14 is rendered novel by the ester groups referred to in claim 1 being present in the compounds used in the method of treatment.

Claims 1 to 15 therefore meet the Novelty requirements of Article 33(2) PCT.

- 3 Examples 10 and 11 of document (A) describe the 1-((1,3-bis-(valyloxy)-2-propoxy) carbonyloxy) ethyl esters of 7-(2-(2-aminothiazoyl-2-methoxyiminoacetamino)-3-cephem-4-carboxylate. Ester derivatives of cepheems under the scope of the present application could be reached from these compounds by removing the amino groups from the valyl moieties.

Documents (B) to (F) describe several other 1-(alkyloxy-carbonyloxy) ethyl esters of carbapenems and cepheems, as well as penicillins, and the use of such groups to improve the bioavailability of beta-lactam type compounds appears to be well known (cf. page 1, lines 27 to 45 of (B)). The presently claimed esters of beta lactams, which are substituted derivatives of 1-(alkoxy-carbonyloxy) ethyl esters, and which bear a structural resemblance to compounds of (A) as described above, would be considered by the skilled man merely to be alternatives to the 1-(alkoxy-carbonyloxy) ethyl ester groups already used in the prior art to improve the bioavailability of beta lactams. Consequently, inventive step (Article 33(3) PCT) could be recognised if the problem of improving the bioavailability of beta-lactams over known ester derivatives of the prior art has been solved. However, there is no data on file to show that this problem is solved. The problem solved by the compounds of the present application seems to be the provision of alternative esters of beta-lactams, and this appears to have been solved in an obvious manner.

Claims 2 to 8, describing preferred embodiments of claim 1, would be patentable only in conjunction with an inventive main claim.

Claim 13 also appears not to be inventive for reasons given above.

Claims 9-12 and 14-15, describing pharmaceutical compositions containing compounds of claim 1, the use of such compounds for the preparation of medicaments, and methods of treatment using said compounds also cannot be considered inventive. The skilled man would expect that the presently claimed esters would have the same pharmacological activity as the parent compounds.

For the assessment of the present claim 14 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII.**

It is noted that the scope of claim 1 covers esters of any known pharmacologically active compound, and it was not feasible to carry out a complete search. The scope of the search was limited to subject matter disclosed in the description according to the Guidelines, B-III, 3.7. This opinion has been limited to the subject matter which was actually searched, i.e. esters of cepheems, penicillins and carbapenems.